DETAILED ACTION

1. Claims 1-18 will be examined on the merits. This application is a 371 of PCT/DE2004/002723, which claims benefit of Foreign Application 103 61 489.3 (Germany), with a priority date of December 23, 2003. However, an English translation of the foreign application has not been submitted, and therefore the priority date of this application is set as the filing date of the PCT application, December 13, 2004.

Claim Objections

2. Claims 1-10 are objected to because of the following informalities: The claims should each be a single sentence and therefore only the first word is capitalized, expect for acronyms such as RNA or proper nouns. Words such as "characterisation" or "homogenisation" should appear as "characterization" or homogenization" to conform to standards for U.S. patents. It is also suggested to use the term "comprising" in place of "characterised" as the connecting term after the preamble. In addition, acronyms such as CNS or GFAP that are not in common use should be spelled out the first time they are used. Commonly used acronyms such as DNA or RNA may be used without further definition. Appropriate correction is required.

Claim 5, 7, 15 and 16 are objected to because these claims contain nucleic acid sequences that are not identified in the claims or specification by a SEQ ID NO. Although these sequences are correctly identified in the Sequence Listing by SEQ ID NO, "reference must be made to the sequence by use of the sequence identifier, preceded by "SEQ ID NO:" in the text of the description or claims, even if the sequence

is also embedded in the text of the description or claims of the patent application" (see MPEP 2422 (d) and 37 CFR 1.821).

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 1-10 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. While minute details are not required in method claims, at least the basic steps must be recited in a positive, active fashion. See Ex parte Erlich, 3 USPQ2d, p. 1011 (Bd. Pat. App. Int. 1986). For example, passive terms such as "preparation", "reverse transcription" and "analysis" should be substituted with active terms such as "preparing", "analyzing" and "reverse transcribing".

In addition, independent claim 1 recites the limitation in section b) "reverse transcription of the RNA in cDNA". It is not clear what is meant by "reverse transcription of the RNA in cDNA" since it is well known in the art that RNA is reverse transcribed to form cDNA, but is not itself comprised in cDNA. For examination purposes, the limitation will be interpreted to mean "reverse transcription of the RNA into cDNA".

Claim 13 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 recites the limitation "the material for the RNA extraction are RNAse-free water, Reverse Transcriptase (RT) buffers, $MgCl_2$, 2'-

Deoxyribonucleoside-5'-triphosphate (dNTP), random hexamers, RNAse inhibitor and reverse transcriptase". It is not clear what is meant by this limitation since RNA extraction processes, as known in the art, would not make use of Reverse Transcriptase (RT) buffers, $MgCl_2$, 2'-Deoxyribonucleoside-5'-triphosphate (dNTP), random hexamers, RNAse inhibitor and reverse transcriptase, which are commonly used for the RT-PCR step following RNA extraction. Therefore, for examination purposes, the limitation will be interpreted to mean "the materials for the RNA extraction and RT-PCR are RNAse-free water, Reverse Transcriptase (RT) buffers, $MgCl_2$, 2'-Deoxyribonucleoside-5'-triphosphate (dNTP), random hexamers, RNAse inhibitor and reverse transcriptase".

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

6. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to

consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

7. Claims 1-4, 9-14, 17 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seyboldt et al. (J. Food Protection (2003) 66:644-651, submitted on IDS of 6/27/2007) in view Raghavendra et al. (J. Pharm. Experiment. Therap. (2003) 306:624-630).

With regard to claims 1 and 10, Seyboldt teaches a method for the species-specific detection of CNS tissue in meat and meat products (a method is provided based on the use of reverse-transcription PCR for tissue-specific and species-specific mRNA detection to identify bovine or other animal CSN tissue in meat and meat products, for overview see Abstract and p. 645, column 1, lines 3-8),

characterized by the steps

a) preparation of the sample material and RNA extraction (organ tissue, including brain tissues, was collected from various animals and RNA was extracted, p. 645, column 1, lines 10-28 and 33-45),

b) reverse transcription of the RNA in cDNA (using the extracted DNA, first strand cDNA synthesis was performed, and PCR primers were then used to amplify the cDNA generated from the neuron-specific GFAP mRNA, p. 645, column 1, line 46 to column 2, line 35) and

c) analysis of the cDNA of the GFAP gene in real-time PCR (the PCR products were analyzed by gel electrophoresis, and were also subjected to RFLP analysis, p. 645, column 2, lines 35-57).

With regard to claim 2, Seyboldt teaches a method characterized by the fact that it is specific to bovine, ovine, caprine and porcine animals (samples for the assay were collected from various tissues from bovine, equine, ovine, porcine and caprine sources, p. 645, column 1, lines 10-19; the assay detects GFAP mRNA from these sources, but not from samples obtained from chicken or turkey brain tissue, p.646, column 2, lines 10-20 and p. 649, column 2, lines 34-42).

With regard to claim 3, Seyboldt teaches a method characterized by the fact that the preparation of the sample material occurs by homogenization, preferably by a combination of vertical rotation movements and horizontal up-and-down movements (brain tissue samples were prepared by homogenization in a blender, p. 645, column 1, lines 22-26).

With regard to claim 4, Seyboldt teaches a method characterized by the fact that the RNA extraction occurs by means of lysis and extraction on phenol basis so that RNA is also extracted from matrices with a particularly high concentration of fatty acids (total RNA was extracted by an optimized guanidinisothiocyanate/phenol RNA extraction method and the RNA recovered after precipitation and washing with alcohol, p. 645, column 1, lines 33-45).

With regard to claim 9, Seyboldt teaches a method characterized by the fact that it is carried out in heat-treated meat and meat products (the stability of GFAP mRNA was tested in retail meat products by heating the meat samples prior to RNA extraction, p. 646, column 1, lines 23-42, p. 648, column 1, lines 11-18 and Table 2).

With regard to claims 11 and 12, Seyboldt teaches a test kit for the species-specific detection of CNS tissue in meat and meat products, containing, at least, material for the species-specific analysis of the GFAP cDNA, containing material for RNA extraction as well as suitable reaction buffers and/or material for the reverse transcription of the extracted GFAP mRNA (materials are provided for the analysis of GFAP cDNA in brain tissue, including the tissue collection, RNA isolation and reverse transcription steps, p. 645, column 1, line 10 to column 2, line 5).

With regard to claim 13, Seyboldt teaches a test kit characterized by the fact that the material for the RNA extraction and RT-PCR are RNAse-free water, Reverse Transcriptase (RT) buffers, $MgCl_2$, 2'-Deoxyribonucleoside-5'-triphosphate (dNTP), random hexamers, RNAse inhibitor and reverse transcriptase (cellular RNA was isolated with the RNA-Pure reagent and the purified RNA was resuspended in RNase-free water, p. 645, column 1, lines 33-45; RT-PCR was carried out using the Superscript first-strand synthesis system using random hexamer primers in a reaction buffer containing dNTPs, $MgCl_2$, an RNase inhibitor and Superscript reverse transcriptase, p. 645, column 1, lines 46-60).

With regard to claim 14, Seyboldt teaches a test kit characterized by the fact that a transcription control is contained in the form of a GFAP mRNA for the supervision of a successful transcription process of the isolated GFAP mRNA into cDNA (positive controls for GFAP mRNA were performed using spinal cord samples, p. 646, column 1, line 59 to column 2, line 2).

With regard to claims 17 and 18, Seyboldt teaches a test kit characterized by the fact that it contains a positive control in the form of the GFAP cDNA of bovine and/or porcine animals, such as a sample with CNS content, and a negative control in the form of the GFAP cDNA of bovine and/or porcine animals (positive controls were performed using spinal cord samples, p. 646, line 59 to column 2, line 2, while negative controls were performed using liver, kidney, spleen, lung or lymph node samples, p. 646, column 2, lines 1-2 and Table 1).

However, Seyboldt does not teach a quantitative detection method based on analysis of the cDNA of the GFAP gene by real-time PCR using an internal amplification control and a dilution series of a reference gene or samples with defined CNS content.

Raghavendra teaches methods for real-time detection of GFAP after spinal cord transection in a rat model test system (see Abstract, p. 625, column 2, line 30 to p. 626, column 1, line 2, p. 627, column 2, lines 5-15 and Figure 2). Raghavendra further teaches that real-time PCR is performed using a dilution series of cDNA obtained from a reverse transcriptase step to generate a standard curve by plotting the threshold values versus the log of the of the amount of total DNA added to the reaction, from which the relative amount of target genes in control and test samples are determined, p. 626, column 1, lines 1-7). An internal amplification control is provided wherein the mRNA levels are normalized to the corresponding GAPDH housekeeping gene levels for controlling variability between samples, p. 628, legend for Table 2).

It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to combine the methods of Seyboldt and Raghavendra since both references teach methods for amplification and detection of GFAP sequences. While Seyboldt teaches detection of GFAP cDNA sequences that may be diagnostic of CNS tissue in meat and meat products, Raghavendra teaches that GFAP sequences may be detected in a quantitative real-time PCR assay. Thus, an ordinary practitioner would have been motivated to use the methods for real time PCR as taught by Raghavendra to replace the gel-based detection techniques of Seyboldt to provide a faster and more quantitative assay of CNS tissue in meat and meat products. Furthermore, the use of sequence specific TaqMan probes as taught by Raghavendra (see Table 1) can detect specific sequences and the relative amounts of different targets directly in the real-time assay (see p. 626, column 1, lines 2-10 and Table 2) as opposed to having to run the secondary RFLP analysis taught by Seyboldt which requires additional enzymatic treatment and further gel electrophoresis (Seyboldt, p. 645, lines 41-57). In addition, the use of fluorescent-labeled probes allows melting curve analysis to be performed to determine the specificity of each primer set and confirmation of the specific PCR products (Raghavendra, p. 626, column 1, line 10 to column 2, line 4).

8. Claims 5, 6 and 15 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seyboldt et al. (J. Food Protection (2003) 66:644-651) in view Raghavendra et al. (J. Pharm. Experiment. Therap. (2003) 306:624-630), as applied to claims 1-4, 9-14, 17

and 18 above, and further in view of Bouchard, P. (GenBank nucleotide submission Y08255 for B. taurus glial fibrillary acidic protein (1996), pp. 1-3) and further in view of Lowe et al. (Nucleic Acids Res. (1990) 18:1757-1761).

Seyboldt and Raghavendra together teach the limitations of claims 1-4, 9-14, 17 and 18, as discussed above. With regard to claim 15, Raghavendra further teaches materials for real-time detection of GFAP after spinal cord transection in a rat model test system (see Abstract, p. 625, column 2, line 30 to p. 626, column 1, line 2, p. 627, column 2, lines 5-15 and Figure 2), including a reaction mixture containing Platinum Taq DNA polymerase, buffer including $MgCl_2$, forward and reverse primers and a Taqman probe labeled with FAM at the 5' end and the fluorescence dye quencher TAMRA at the 3' end, specific to GFAP (p. 625, column 2, line 64 to p. 626, column 1, line 1 and Table 1).

However, neither Seyboldt nor Raghavendra teach a method characterized by the fact that the real-time PCR is carried out for bovine, ovine and caprine animals with primer RTGcowM56F2a 5'-ACC TGC GAC CTG GAG TCC T-3', primer RTGcowM56R2a 5'-CTC GCG CAT CTG CCG-3' and TaqManrngb sensor OptiR 6-FAM-ACT CGT TCG TGC CGC GC-MGB, or provide a test kit characterized by the fact that the material for the reverse transcription of the extracted GFAP mRNA for the detection of bovine, ovine and caprine animals are primer RTGcowM56F2a, primer RTGcowM56R2a and TaqManmgb sensor OptiR.

Bouchard teaches the nucleotide sequence of the mRNA for bovine GFAP, wherein primer RTGcowM56F2a (SEQ ID NO: 1) is 100% homologous to positions 865-

883 (see below), primer RTGcowM56R2a (SEQ ID NO: 2) is 100% homologous to positions 924-910 (see below), and TaqManrngb sensor OptiR (SEQ ID NO: 3) is 100% homologous to positions 901-885 (see below) (see Bouchard for entire 1287-bp sequence of bovine GFAP).

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RESULT 3
Y08255
LOCUS       Y08255                  1287 bp    mRNA    linear   MAM 18-APR-2005
DEFINITION  B.taurus mRNA for glial fibrillary acidic protein.
ACCESSION   Y08255
VERSION     Y08255.1  GI:1561570
KEYWORDS    glial fibrillary acidic protein.
SOURCE      Bos taurus (cattle)
  ORGANISM  Bos taurus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Laurasiatheria; Cetartiodactyla; Ruminantia;
            Pecora; Bovidae; Bovinae; Bos.
REFERENCE   1
  AUTHORS   Bouchard,P.
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 1287)
  AUTHORS   Bouchard,P.
  TITLE     Direct Submission
  JOURNAL   Submitted (19-SEP-1996) P. Bouchard, Universite Blaise Pascal, URA
            CNRS 1944 Biologie des Protistes, 24 Avenue des Landais, Les
            Cezeaux, 63177 Aubiere Cedex, FRANCE
ORIGIN

  Query Match             100.0%;  Score 19;  DB 8;  Length 1287;
  Best Local Similarity   100.0%;
  Matches   19;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 ACCTGCGACCTGGAGTCCT 19
              |||||||||||||||||||
Db        865 ACCTGCGACCTGGAGTCCT 883



RESULT 15
Y08255/c
LOCUS       Y08255                  1287 bp    mRNA    linear   MAM 18-APR-2005
DEFINITION  B.taurus mRNA for glial fibrillary acidic protein.
ACCESSION   Y08255
VERSION     Y08255.1  GI:1561570
KEYWORDS    glial fibrillary acidic protein.
SOURCE      Bos taurus (cattle)
  ORGANISM  Bos taurus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Laurasiatheria; Cetartiodactyla; Ruminantia;
            Pecora; Bovidae; Bovinae; Bos.
REFERENCE   1
  AUTHORS   Bouchard,P.
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 1287)
  AUTHORS   Bouchard,P.
  TITLE     Direct Submission
  JOURNAL   Submitted (19-SEP-1996) P. Bouchard, Universite Blaise Pascal, URA
            CNRS 1944 Biologie des Protistes, 24 Avenue des Landais, Les
            Cezeaux, 63177 Aubiere Cedex, FRANCE
ORIGIN
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  Query Match             100.0%;  Score 15;  DB 8;  Length 1287;
  Best Local Similarity   100.0%;
  Matches   15;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 CTCGCGCATCTGCCG 15
              ||||||||||||||||
Db        924 CTCGCGCATCTGCCG 910


RESULT 13
Y08255/c
LOCUS       Y08255                  1287 bp    mRNA    linear   MAM 18-APR-2005
DEFINITION  B.taurus mRNA for glial fibrillary acidic protein.
ACCESSION   Y08255
VERSION     Y08255.1  GI:1561570
KEYWORDS    glial fibrillary acidic protein.
SOURCE      Bos taurus (cattle)
  ORGANISM  Bos taurus
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Laurasiatheria; Cetartiodactyla; Ruminantia;
            Pecora; Bovidae; Bovinae; Bos.
REFERENCE   1
  AUTHORS   Bouchard,P.
  JOURNAL   Unpublished
REFERENCE   2  (bases 1 to 1287)
  AUTHORS   Bouchard,P.
  TITLE     Direct Submission
  JOURNAL   Submitted (19-SEP-1996) P. Bouchard, Universite Blaise Pascal, URA
            CNRS 1944 Biologie des Protistes, 24 Avenue des Landais, Les
            Cezeaux, 63177 Aubiere Cedex, FRANCE
ORIGIN

  Query Match             100.0%;  Score 17;  DB 8;  Length 1287;
  Best Local Similarity   100.0%;
  Matches   17;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 ACTCGTTCGTGCCGCGC 17
              |||||||||||||||||
Db        901 ACTCGTTCGTGCCGCGC 885
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It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to design amplification primers for real-time PCR detection of the bovine GFAP cDNA based on the sequence taught by Bouchard (see p. 2) since this sequence was known at the time of the invention, and represents a gene target highly useful for detection of bovine CNS tissue in meat and meat products (Seyboldt, p. 648, column 2, line 37 to p. 649, column 1, line 7). Thus, an ordinary practitioner would have been motivated to use such a sequence in order to design primers and a labeled probe that are specific for the bovine cDNA GFAP sequence.

Furthermore, Raghavendra has shown that primers and TaqMan-type probes can be designed to detect GFAP sequences in a real-time quantitative PCR assay (Raghavendra, p. 625, column 2, line 30 to p. 626, column 1, line 2). Moreover, software programs for designing primers and probes for real-time PCR were well known at the time of the invention.

In the recent court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

Since the claimed primers and probe simply represent structural homologs of the cDNA sequence taught by Bouchard , which are 100% derived from sequences expressly suggested by the prior art of Bouchard as useful for amplification and detection of bovine GFAP cDNA and concerning which a biochemist of ordinary skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents at the time the invention was made, as shown in Lowe, one of skill in the art was clearly aware of the factors involved in designing amplification primers from a known sequence, and would have routinely and predictably designed any such primers. Specifically, Lowe teaches a computer program based on a set of rules which take into account both the sequence of the primers and the amplified region of DNA, such that primer-to-target hybridization is enhanced, while facilitating attainment of full-length extension products by minimizing non-specific product formation and self-priming (see Abstract and p. 1757, column 2, line 33 to p. 1758, column 1, line 41). The program has been tested on a variety of gene products for RT-PCR, for both total and cytoplasmic RNA samples prepared by several different methods (Lowe, p. 1758, column 2, last 2 lines). "Experimental testing has shown that all the amplification products specified by these primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe" (Lowe, p. 1769, column 2, line 4-8).

9. Claims 7, 8 and 16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Seyboldt et al. (J. Food Protection (2003) 66:644-651) in view Raghavendra et al. (J. Pharm. Experiment. Therap. (2003) 306:624-630), as applied to claims 1-4, 9-14, 17 and 18 above, and further in view of Fahrenkrug et al. (Mammalian Genome (2002) 13:475-478) and GenBank nucleotide submission BF443658 (Fahrenkrug, for pig cDNA mRNA sequence (2000), pp. 1-3).

Seyboldt and Raghavendra together teach the limitations of claims 1-4, 9-14, 17 and 18, as discussed above. With regard to claim 16, Raghavendra further teaches materials for real-time detection of GFAP after spinal cord transection in a rat model test system (see Abstract, p. 625, column 2, line 30 to p. 626, column 1, line 2, p. 627, column 2, lines 5-15 and Figure 2), including a reaction mixture containing Platinum Taq DNA polymerase, buffer including $MgCl_2$, forward and reverse primers and a Taqman probe labeled with FAM at the 5' end and the fluorescence dye quencher TAMRA at the 3' end, specific to GFAP (p. 625, column 2, line 64 to p. 626, column 1, line 1 and Table 1).

However, neither Seyboldt nor Raghavendra teach a method characterized by the fact that the real-time PCR is carried out for porcine animals with the following primers: primer RTGpigM56F2 5'-GAC CTG CGA CGT GGA GTC CC-3', primer RTGpigM56R2 5"-TGG CGC TCC TCC TGC TCC -3' and TaqManrngb sensor OptiR 6-FAM-ACT CGT TCG TGC CGC GC-MGB, or provide a test kit characterized by the fact that the material for reverse transcription of the extracted GFAP mRNA for the detection

of porcine animals are primer RTGpigM56F2, primer RTGpigM56R2 and TaqManmgb sensor OptiR.

Fahrenkrug and GenBank nucleotide submission BF443658 teaches the EST nucleotide sequence of the mRNA for porcine GFAP, wherein primer RTGpigM56F2 (SEQ ID NO: 4) is 100% homologous to positions 114-95 (see below), primer RTGpigM56R2 (SEQ ID NO: 5) is 100% homologous to positions 40-57 (see below), and TaqManrngb sensor OptiR (SEQ ID NO: 6) is 100% homologous to positions 77-93 (note: SEQ ID NO: 3 is identical to SEQ ID NO: 6) (see GenBank nucleotide submission BF443658 for entire EST sequence that includes porcine GFAP).

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RESULT 3
BF443658/c
LOCUS       BF443658                338 bp    mRNA    linear   EST 09-MAY-2010
DEFINITION  261236 MARC 2PIG Sus scrofa cDNA 5', mRNA sequence.
ACCESSION   BF443658
VERSION     BF443658.1  GI:11503750
KEYWORDS    EST.
SOURCE      Sus scrofa (pig)
  ORGANISM  Sus scrofa
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Laurasiatheria; Cetartiodactyla; Suina; Suidae;
            Sus.
REFERENCE   1  (bases 1 to 338)
  AUTHORS   Fahrenkrug,S.C., Smith,T.P.L., Freking,B.A., Cho,J., White,J.,
            Vallet,J., Wise,T., Rohrer,G.A., Pertea,G., Sultana,R.,
            Quackenbush,J. and Keele,J.W.
  TITLE     Porcine gene discovery by normalized cDNA-library sequencing and
            EST cluster assembly
  JOURNAL   Mamm. Genome 13 (8), 475-478 (2002)
   PUBMED   12226715
COMMENT     Contact: Smith TPL
            USDA, ARS, US Meat Animal Research Center
            PO Box 166, Clay Center, NE 68933-0166, USA
            Tel: 402 762 4366
            Fax: 402 762 4390
            Email: Tim.Smith@ars.usda.gov
            Single pass sequencing. Bases called and alt_trimmed with phred
            v0.980904.e. Vector identified by cross_match with the -minscore 18
            and -minmatch 12 options.
            PCR PRimers
            FORWARD: AGGAAACAGCTATGACCAT
            BACKWARD: GTTTTCCCAGTCACGACG
            Plate: 94  row: F  column: 16
            Seq primer: ATTTAGGTGACACTATAG.
ORIGIN

  Query Match             100.0%;  Score 20;  DB 3;  Length 338;
  Best Local Similarity   100.0%;
  Matches   20;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;
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Qy          1 GACCTGCGACGTGGAGTCCC 20
              ||||||||||||||||||||
Db        114 GACCTGCGACGTGGAGTCCC 95



RESULT 3
BF443658
LOCUS       BF443658                338 bp    mRNA    linear   EST 09-MAY-2010
DEFINITION  261236 MARC 2PIG Sus scrofa cDNA 5', mRNA sequence.
ACCESSION   BF443658
VERSION     BF443658.1  GI:11503750
KEYWORDS    EST.
SOURCE      Sus scrofa (pig)
  ORGANISM  Sus scrofa
            Eukaryota; Metazoa; Chordata; Craniata; Vertebrata; Euteleostomi;
            Mammalia; Eutheria; Laurasiatheria; Cetartiodactyla; Suina; Suidae;
            Sus.
REFERENCE   1  (bases 1 to 338)
  AUTHORS   Fahrenkrug,S.C., Smith,T.P.L., Freking,B.A., Cho,J., White,J.,
            Vallet,J., Wise,T., Rohrer,G.A., Pertea,G., Sultana,R.,
            Quackenbush,J. and Keele,J.W.
  TITLE     Porcine gene discovery by normalized cDNA-library sequencing and
            EST cluster assembly
  JOURNAL   Mamm. Genome 13 (8), 475-478 (2002)
   PUBMED   12226715
COMMENT     Contact: Smith TPL
            USDA, ARS, US Meat Animal Research Center
            PO Box 166, Clay Center, NE 68933-0166, USA
            Tel: 402 762 4366
            Fax: 402 762 4390
            Email: Tim.Smith@ars.usda.gov
            Single pass sequencing. Bases called and alt_trimmed with phred
            v0.980904.e. Vector identified by cross_match with the -minscore 18
            and -minmatch 12 options.
            PCR PRimers
            FORWARD: AGGAAACAGCTATGACCAT
            BACKWARD: GTTTTCCCAGTCACGACG
            Plate: 94  row: F  column: 16
            Seq primer: ATTTAGGTGACACTATAG.

ORIGIN

  Query Match             100.0%;  Score 18;  DB 3;  Length 338;
  Best Local Similarity   100.0%;
  Matches   18;  Conservative    0;  Mismatches    0;  Indels    0;  Gaps    0;

Qy          1 TGGCGCTCCTCCTGCTCC 18
              ||||||||||||||||||
Db         40 TGGCGCTCCTCCTGCTCC 57
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It would have been prima facie obvious to one having ordinary skill in the art at the time the invention was made to design amplification primers for real-time PCR detection of the porcine GFAP cDNA based on the sequence taught by Fahrenkrug and GenBank nucleotide submission BF443658 (see p. 1) since this sequence was known at the time of the invention, and represents a gene target highly useful for detection of

related sequences found in bovine CNS tissue in meat and meat products (Seyboldt, p. 648, column 2, line 37 to p. 649, column 1, line 7). Thus, an ordinary practitioner would have been motivated to use such a sequence in order to design primers and a labeled probe that are specific for porcine GFAP cDNA sequences. Furthermore, Raghavendra has shown that primers and TaqMan-type probes can be designed to detect GFAP sequences in a real-time quantitative PCR assay (Raghavendra, p. 625, column 2, line 30 to p. 626, column 1, line 2). Moreover, software programs for designing primers and probes for real-time PCR were well known at the time of the invention.

In the recent court decision *KSR International Co. v. Teleflex Inc., 82* 127 SCt 1727 (2007), the U.S. Supreme Court determined that if the combination of the claimed elements was "obvious to try" by a person of ordinary skill, this might show that such a combination was obvious under §103. Regarding "obvious to try", the Court stated:

"A person of ordinary skill is also a person of ordinary creativity, not an automaton. The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "obvious to try." Id., at 289 (internal quotation marks omitted). When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103."

Since the claimed primers and probe simply represent structural homologs of the cDNA sequence taught by Fahrenkrug and GenBank nucleotide submission BF443658, which are 100% derived from sequences expressly suggested by the prior art of Fahrenkrug and GenBank nucleotide submission BF443658 as useful for amplification and detection of porcine GFAP cDNA and concerning which a biochemist of ordinary

skill would attempt to obtain alternate compounds with improved properties, the claimed primers are *prima facie* obvious over the cited references in the absence of secondary considerations.

With regard to the issue of equivalence of the primers, MPEP 2144.06 notes "Substituting equivalents known for the same purpose. In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout , 675 F.2d 297, 213 USPQ 532 (CCPA 1982)."

With regard to the issue of reasonable expectation of success in using such equivalents at the time the invention was made, as shown in Lowe, one of skill in the art was clearly aware of the factors involved in designing amplification primers from a known sequence, and would have routinely and predictably designed any such primers. Specifically, Lowe teaches a computer program based on a set of rules which take into account both the sequence of the primers and the amplified region of DNA, such that primer-to-target hybridization is enhanced, while facilitating attainment of full-length extension products by minimizing non-specific product formation and self-priming (see Abstract and p. 1757, column 2, line 33 to p. 1758, column 1, line 41). The program has been tested on a variety of gene products for RT-PCR, for both total and cytoplasmic RNA samples prepared by several different methods (Lowe, p. 1758, column 2, last 2

lines). "Experimental testing has shown that all the amplification products specified by these primers are of the predicted size and also hybridize with the appropriate cDNA or internal oligonucleotide probe" (Lowe, p. 1769, column 2, line 4-8).

Conclusion

10. Claims 1-18 are rejected. No claims are allowable.

Correspondence

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637